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Intrinsic Defects in the Fetal Alcohol Syndrome: Studies on 76 Cases from British Columbia and the Yukon Territory

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SMITH, D. F., G. G. SANDOR, P. M. MACLEOD, S. TREDWELL, B. WOOD AND D. E. NEWMAN. *Intrinsic defects in the fetal alcohol syndrome: Studies on 76 cases from British Columbia and the Yukon Territory*. NEUROBEHAV. TOXICOL. TERATOL. 3(2) 145–152, 1981.—Children diagnosed as FAS using standard criteria of maternal alcoholism, poor growth, delayed development and characteristic facial appearance underwent an investigative protocol involving skeletal x-ray surveys, cardiac assessments and intravenous pyelograms (IVP). Significant skeletal findings included cervical spine fusion in 20 of 46 children (43%), x-ray confirmation of microcephaly in 26/49 (53%) and abnormal thoracic cage development in 13/48 (27%). Thirty-nine of 54 children (72%) demonstrated a characteristic tapering of the shaft and occasional associated prominence of the tuft of the distal phalanges. Bone age was delayed 2 standard deviations or greater in 14 of 51 children (27%). Cardiac lesions were found in 31 of 76 (41%) and a further 12 (16%) had functional murmurs. Lesions were ventricular septal defect 20 (26%), Tetralogy of Fallot 4 (5.1%), plus a variety of less frequent abnormalities. IVP's were limited to 19 random cases with 5 (26%) showing alterations from the normal. Cervical spine abnormalities of FAS as compared to the Klippel-Feil Syndrome are dissimilar and probably represent a different entity. Hand and lateral cervical spine x-ray studies are felt to be a useful adjunct to the diagnosis and management of the fetal alcohol syndrome.

Birth defects Fetal alcohol syndrome Skeletal defects Congenital heart disease Klippel-Feil syndrome

OVER the past twelve years since the initial description of alcohol- affected children by Lemoine *et al.* [12], and later work by Ulleland [22] and Jones *et al.* [11] with the designated term "Fetal Alcohol Syndrome" (FAS) in 1974, a wide spectrum of clinical presentations have been documented. Major findings have emphasized poor growth, delayed development reflecting brain maldevelopment and a characteristic facial appearance in association with maternal alcoholism during pregnancy.

High numbers of children with FAS presenting in British Columbia have allowed detailed clinical investigations. Children fulfilling standard criteria for diagnosis have undergone skeletal surveys, intravenous pyelograms and cardiac assessments as part of a wider ranging clinical investigative study of FAS.

The skeletal surveys were instituted following reports of skeletal abnormalities in newborn mice related to maternal alcohol consumption. Areas of abnormalities in the mouse [2] included defective occipital bones with low dietary alcohol levels, plus sternal and rib abnormalities at higher levels. The need for cardiac assessments was based on previous clinical studies plus the suspicion of possible undiagnosed heart problems in affected children.

METHOD

All patients were investigated either at the Health Centre for Children or at the Children's Hospital in Vancouver. Both hospitals are teaching hopsitals of the University of British Columbia and undertake primary, secondary and ter-

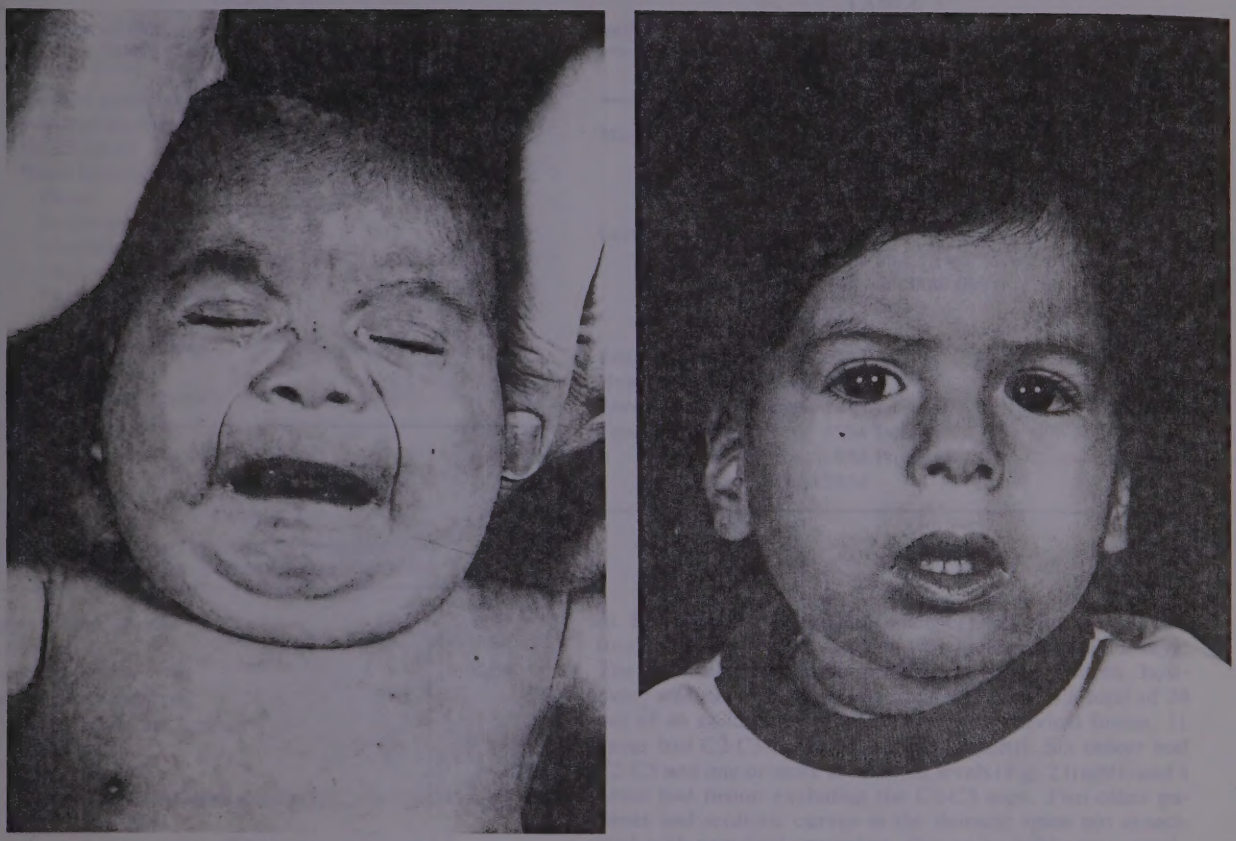


FIG. 1. Facial features seen in the fetal alcohol syndrome. (left) Characteristic facial appearance of a native Indian infant with FAS. Note small palpebral fissures, thin vermilion border to lip, low hair line. (right) Facial features of a 3-year-old male child with FAS.

tiary care. All cardiac cases were seen at the Health Centre for Children where most cardiac assessments and all pediatric cardiac surgery are performed. All x-rays were reported by either of two pediatric radiologists affiliated with the University of British Columbia.

The diagnosis of all 76 cases was based on a history of heavy maternal alcoholic consumption during the pregnancy with clinical findings in the child of characteristic facial appearance (Fig. 1) and poor growth performance (Table 1). Developmental delay was usually confirmed on pediatric neurological assessment or on an educational-psychological assessment in the child over five years of age. The majority of children showed other varying morphological abnormalities (Table 2).

Skeletal x-ray studies excluded most newborns due to a relatively low initial yield, probably reflecting limited skeletal ossification. Later in the study x-rays on some patients were limited to cervical spine, hand and wrist, as well as chest, reflecting a greater positive yield from these specific areas.

The total number of IVP's was also limited in view of few findings of major significance in the initial numbers studied.

TABLE 1

FETAL ALCOHOL SYNDROME

Clinical Criteria for Study Patients
1. Confirmation history of heavy maternal alcohol consumption during gestation period.
2. Alteration in brain function.
3. Poor growth performance.
4. Characteristic facial appearance.

The cardiac assessment was generally carried out by one of the pediatric cardiologists. The standard cardiac assessment consisted of physical examination, chext x-ray, electrocardiogram, and later in the series echocardiography. Cardiac catheterizations were performed on a few patients when indicated hemodynamically or when there was doubt

TABLE 2

COMMON CLINICAL FINDINGS IN 56 STUDY PATIENTS (GREATER THAN 50% INCIDENCE)

Prenatal growth deficiency
Postnatal growth deficiency
Microcephaly
Facial alterations
Ptosis
Strabismus
Microphthalmia
Short upturned nose
Flattened philtrum
Low hair line
Developmental delay
Hyperactivity
Native Indian ancestry

TABLE 3

BONE ABNORMALITIES IN FAS BASED ON SKELETAL SURVEYS

		Percentage
Microcephaly	20/49 Definite 6/49 Mild	
	Total 26/49	54%
Cervical spine abnormalities	17/38 on Cervical views 3/8 on Skull films	
	Total 20/46	43%
Radial ulnar synostosis	2/43	
Hypoplastic radial head	8/43	
Abnormal thoracic cage	13/48	27%
Tapering terminal phalanges	35/54 Definite 4/54 Probable	
	Total 39/54	72%

TABLE 4

FETAL ALCOHOL SYNDROME
ADDITIONAL RADIOLOGICAL FINDINGS

Congenital heart disease on chest x-ray	18/48
Short middle phalanx, 5th digit and/or clinodactyly	12/54
Isolated single case findings	
Club foot (3)	
Short great toe	
Valgus distal phalangeal great toe	
S2,3 Spina bifida	
Congenital anomalies of the bodies of L2 and L3	
Pes planus	
Congenital dislocated hip	
Dislocated interphalangeal joint of the thumb	

bout the clinical diagnosis. Cardiac follow-up varied from 0 o 6 years with some limitations imposed by social problems nherent in the families of some of the patients. Patients as-essed included direct referrals where a cardiac lesion was uspected or routine investigations on children whose cardiac atus appeared clinically normal on physical examination.

RESULTS

All 76 patients in the study were clinically assessed by the rdiology and medical staff. Lesser numbers (54) were as-essed from the x-ray standpoint as newborn studies were nited. The ages ranged from birth to eighteen years and in e total series 43 males and 33 females were studied. Only 7 tients were of Caucasian descent, with the remainder of e children having North American Indian mothers with thers of native Indian or Caucasian ancestry. No other cial groups were represented in the series.

diographic Study

Skeletal abnormalities or variations from the normal ap-arance were seen in the majority of children studied (Table 3). Radiographic evidence of microcephaly was present in a total of 26 of 49 (54%) children who underwent skull x-rays. The most unexpected abnormality in these children, however, was cervical spine abnormalities seen in a total of 20 out of 46 children (43%). Of those with cervical fusion, 11 cases had C2-C3 fusion alone (Fig. 2 (left)). Six others had C2-C3 and one or more associated levels (Fig. 2 (right)) and 3 cases had fusion excluding the C2-C3 area. Two other patients had scoliotic curves in the thoracic spine not associated with vertebral anomalies. One spina bifida was noted.

Forearm radiographs showed radioulnar synostosis in 2 of 43 patients (Fig. 3), with an additional 8 children showing a hypoplastic radial head.

An abnormal thoracic cage was seen in 13 of 48 children (27%). Changes included 2 children with pigeon chest, 1 with funnel chest, 1 thoracic lordosis, 7 with rib anomalies (generally hypoplastic ribs or fused ribs) and 2 eventrations of the diaphragm. Congenital heart disease was noted on 18 of 48 chest x-rays (38%).

The most common feature noted on the skeletal surveys, was tapering of the terminal phalanges seen in 39 of 54 patients (72%) (Fig. 4 (left)). The index and little finger were prominently involved (Fig. 3 (right)).

The tapering of the terminal phalanges was compared in two age groups, under 2 and over 2. No significant difference was noted in the two groups with 12 of 18 (67%) less than two years showing positive results and 15 of 24 (63%) being positive in the group older than 2 years, in 42 initial patients studied. A short middle phalanx of the fifth digit and/or clinodactyly was noted in 12 of 54 children, a finding also seen frequently in normal native Indian children.

Using the method of Greulich and Pyle [8], skeletal maturation was assessed in 51 children with a total of 14 or (27%) showing a delay of two standard deviations or greater.

An additional radiological finding included a club foot reported in three children. Isolated single case findings included a short great toe, a valgus distal phalangeal great toe, and S2-S3 spina bifida, congenital anomalies of the bodies of L2-L3, pes planus, a congenital dislocated hip, and a dislocated interphalangeal joint of the thumb (Table 4).

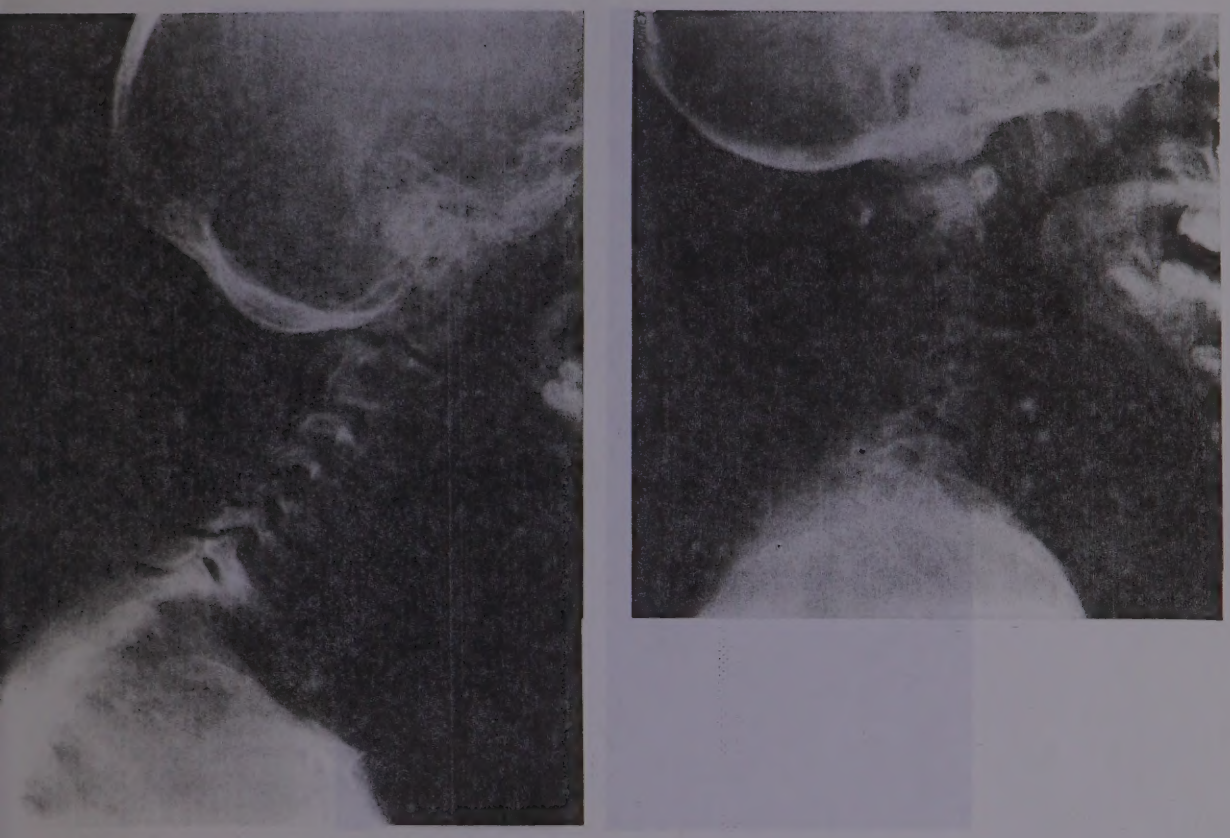


FIG. 2. Two examples of cervical spine fusion seen in FAS children. (left) Fusion of C2-C3. (right) Fusion of the bodies of C2, C3, C4 with fusion of posterior elements.

Intravenous pyelograms in 19 children revealed two children with mild ureteropelvic obstruction, one with a neurogenic bladder secondary to meningomyelocoele and one with minor malrotation of the left kidney. A fifth child had a duplicated left renal pelvis.

In a separate parallel study the cervical spine anomalies were reviewed by a pediatric orthopedic surgeon and compared to the known associated anomalies seen in the Klippel-Feil Syndrome. With exclusion of incomplete and poorer quality films and also exclusion of studies on infants under 4 months, 36 cervical spine films were evaluated. Of these, 19 showed cervical spine fusion (53%), a higher percentage compared to the radiological screen (43%) of FAS patients.

Cardiac Examination

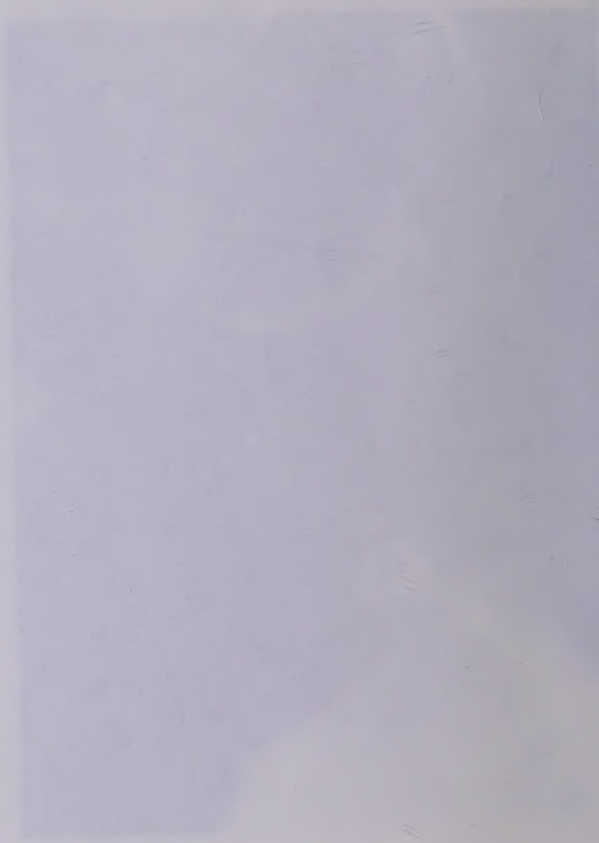
Cardiac lesions were present in 31 patients (41%) and a further 12 (16%) had functional murmurs (Table 5). There were 20 patients with ventricular septal defects (VSD); 10 were confirmed on cardiac catheterization and in 10 the diagnosis was made on the characteristic clinical findings in patients in whom there were no hemodynamic indications for catheterization. Of this group with VSD's, 15 were simple

TABLE 5

CARDIAC MALFORMATIONS IN THE FETAL ALCOHOL SYNDROME

Total number of patients	=	76
Males	=	43
Females	=	33
	Number	Percent
Patients with cardiac malformations	31	41
Patients with functional murmurs	12	16

VSD's and 5 were complex (Table 6). Other lesions included Tetralogy of Fallot in 4 patients (5%) and atrial septal defects in 3 (1 associated with VSD). Two patients were noted with coarctation of the aorta, both associated with VSD, and 1 of these had a small left ventricle and mitral valve. There was 1 patient with a VSD with aortic valve regurgitation due to prolapse of an aortic cusp through the ventricular septal defect. A further patient had both sub-aortic and sub-pulmonary obstruction in association with VSD. Two patients had peripheral pulmonary stenosis and another had



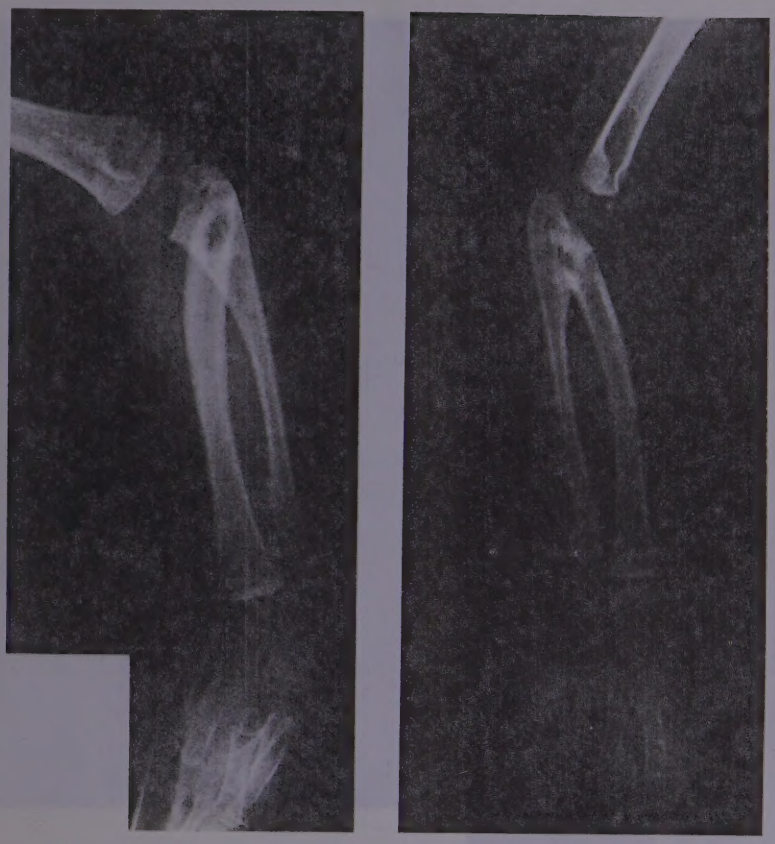


FIG. 3. Two views of radio-ulnar synostosis seen in FAS children. (left) Lateral view. (right) Antero-posterior view. Note the fusion of radius and ulna at the proximal end of both bones.

TABLE 6
VENTRICULAR SEPTAL DEFECTS

		Number
nple VSD (1 with mesocardia)	=	15
VSD + subpulmonary and subaortic stenosis	=	1
VSD + aortic regurgitation	=	1
VSD + coarctation	=	1
VSD + coarctation + small L.V. + mitral	=	1
VSD + 2°ASD	=	1
	Total	20

pulmonary atresia with a double outlet right ventricle. Dextro-cardia (with VSD) and mesocardia (with VSD) both occurred once. One premature infant with a patent ductus arteriosus developed irreversible pulmonary hypertension at one year of age and a further patient may have right heart problems secondary to pulmonary disease.

Changes in the electrocardiogram, chest x-ray and echo-cardiogram reflected the underlying abnormal hemodynamics. In one patient a counter-clockwise loop and abnormal repolarization were found. This patient subsequently suffered a "crib" death and it is possible that an arrhythmia may have occurred.

Most simple VSD's were small and only 3 out of 15 required surgery. A total of 13 patients require or have had surgery. The patient with pulmonary stresia and double outlet right ventricle died shortly after birth before any medical or surgical intervention.

DISCUSSION

A variety of animal studies have demonstrated the adverse effects of alcohol on the developing fetus [2, 16, 17, 18,

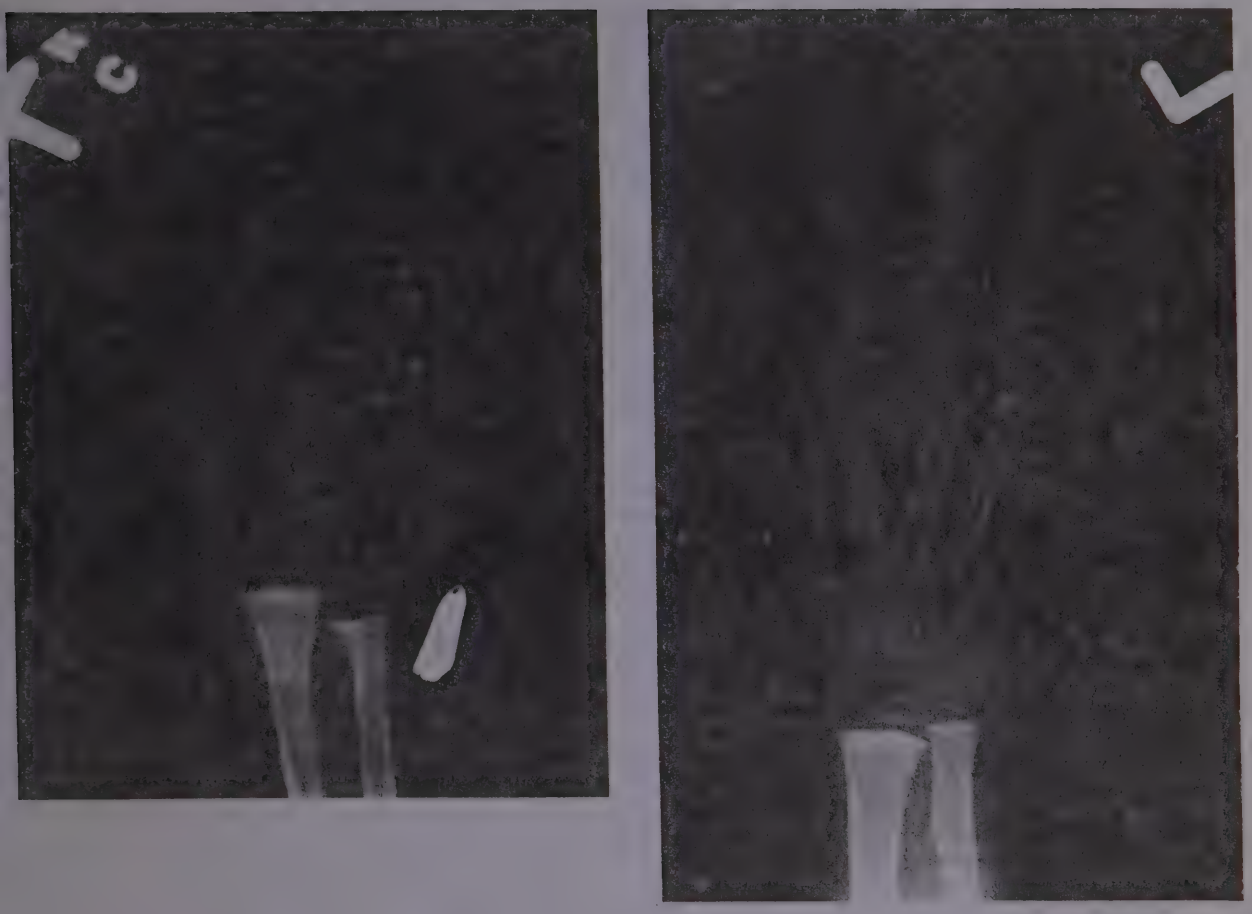


FIG. 4. Two examples of phalangeal changes in FAS. (left) A 1½-year-old child's hand showing narrowing, tapering and tufting of the tips of the distal phalanges. Bone age 1 year. (right) A 2½-year-old child's hand showing narrowing, attenuation and tufting of the distal phalanges with a hypoplastic terminal phalanx of the 5th finger. Bone age 1 year, 6 months.

TABLE 7

TYPES AND FREQUENCY OF SKELETAL ANOMALIES IN THE MOUSE MODEL OF FAS [2]

Strain	Diet (%EDC)	Total Fetuses Examined	Occiput	Sternum	Ribs	Total Abnormal (%)
CBA	Lab Chow	15	1	0	0	7
	0	18	0	0	0	0
	15	6	6	3	0	100
	20	6	6	6	4	100
	25	5	5	5	3	100
C3H	Lab Chow	35	2	0	0	6
	0	24	1	0	0	4
	20	22	18	6	5	82
	25	16	16	7	9	100
	30	6	6	4	6	100

21]. Chernoff [2] developed an animal model for FAS using CBA and C3H strains of mice. He demonstrated both dose and strain variable responses in the fetuses of impregnated mice receiving 15% to 35% proportions of ethanol derived calories in the diet. His findings of occipital bone abnormalities at lower alcohol levels with sternal and rib abnormalities at higher levels correlates well with skeletal abnormalities in this study, with the exception of cervical spine defects in the human which replaced occipital defects in the mouse (Table 7).

In a similar comparison the frequency of cardiac lesions in the same mouse study increased with high alcohol intake in both strains, the most common abnormalities being ventricular septal defects and hemopericardium. Randall *et al.* [16] used an additional mouse strain (C57B1/G3) and produced eleven of sixteen fetuses with cardiac problems including great vessel and venocaval anomalies, atresia of the mitral valve and again intra-ventricular septal defects. Clarren and Smith noted murmurs and atrial septal defects to be the most frequent cardiac lesions in the human with occasional findings of ventricular septal defects, Tetralogy of Fallot and great vessel anomalies. Frequency of cardiac lesions varied from 29% to 50% in human studies [3, 9, 13, 23].

In our patients the frequency of cardiac malformations was 41% with an additional 16% felt to have functional murmurs. As cardiac catheterizations were not carried out on all patients, some of the functional murmurs and simple ventricular septal defects may have been reversed, a frequent difficulty in borderline murmur situations. The frequency of cardiac lesions conforms with that found in other series.

The most frequent type of cardiac malformation in our series was a simple VSD, which differs from some reports [3, 12, 22], but correlates well with the animal models [2,15]. Complex VSD's and Tetralogy of Fallot were also found more frequently than secondary ASD's. These and other malformations represent abnormalities of septation, conal malalignment, right- and left-sided outflow obstructions and disorders of cardiac situs. This suggests a non-specific teratogenic effect of alcohol or its metabolites.

Our renal findings were minimal. No patient showed abnormal serum creatinines or raised blood urea nitrogens and the findings of malobstruction or malrotation were considered minimal. Patients were selected at random for IVP's and our findings indicate little justification for the IVP as a screening procedure in patients with FAS. Other series [3, 4, 7], however, have reported more serious problems such as hydronephrosis. Ultrasound may prove eventually to be a reliable alternative to the IVP for assessment of renal and urinary tract structure in FAS children.

Due to the relative high yield of abnormal phalangeal appearance (72%) and cervical spine fusion (43%) radiological examination of these areas is helpful in supporting the diagnosis. Significantly, only two children of the 20 with cervical vertebral fusion were noted clinically to have an unusual neck appearance. X-rays of the cervical spine are not recommended for children under one year as no positive findings were noted in our series in this age group. One child, initially negative in studies under one year, showed cervical fusion five years later on repeat x-rays.

While only children with full features of FAS are included, it should be noted that three additional children born to alcoholic mothers but with no significant growth defects have shown similar cervical spine fusion on screening. Both Caucasian and native Indians have shown the skeletal abnormalies, while a study of 15 non-FAS native Indian children receiving skeletal surveys for child abuse or as part of a leukemic protocol have failed to show tapering of the distal phalanges or other changes.

In spite of similarities, Klippel-Feil and Fetal Alcohol Syndrome seem to be separate entities. The classic Klippel-Feil Syndrome has a single level fusion in 20% of 418 cases reported by Gray in 1964 and four or more levels in 50%. In contrast in our FAS cases, a single fusion was found in 53% and four or more levels involved in only 16%. The major visceral anomaly in the Klippel-Feil Syndrome is seen in the genitourinary system reported in various series as between 35% and 60%. Cardiovascular anomalies in the Klippel- Feil Syndrome have been reported in the range of 14%. The major visceral anomalies, on the other hand, in our FAS cases are in the cardiovascular system with 41% showing congenital heart disease. Genitourinary anomalies in our series were minor and few [2].

The patient with Klippel-Feil Syndrome usually has normal intelligence although problems in coordination have been reported. The Fetal Alcohol Syndrome, on the other hand, is characterized by developmental delay and frequent mental retardation in association with microcephaly. The phalangeal abnormalities seen in our FAS series are not reported in the Klippel-Feil Syndrome.

Both the Klippel-Feil anomaly and the cervical fusion seen in the Fetal Alcohol Syndrome correspond well to a teratogenic insult at a specific stage of intrauterine development between the 24th and 28th day of fetal life. As the etiology of the Klippel-Feil Syndrome is not known, there may be an overlap between these two conditions. Clearly further work is required in the study of the curious parallels.

The true frequency of this Syndrome is undetermined, but estimates have been as high as 1–2 live births per 1000 with up to 3–5 live births showing partial expression [3]. As a tertiary referral base, the Department of Pediatrics of the University of British Columbia through its two hospitals may see only the more serious FAS cases which could give a distorted view of affected children. With only $2^1/_2$% of the population in British Columbia being native Indian, our statistics reveal a 10.9 to 1 ratio of native Indian children to Caucasian from our population with FAS. This raises the significance of racial susceptibility to the teratogenic effects of alcohol, a very difficult point to satisfactorily answer [1,16].

The question of the role of the different metabolic pathways of alcohol [6,20] and possible deleterious effects of acetaldehyde rather than ethyl alcohol has yet to be clarified. Further work may determine susceptibility of different maternal genotypes and give rise to selection of prospective mothers at risk.

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